PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Application of: Stephen A. Johnston et al Serial No. 10/023,437 Filing Date: December 17, 2001 Art Unit: 1645 Examiner: Vanessa L. Ford Methods and Compositions for Vaccination Comprising Nucleic Acid and/or Polypeptide Sequences of Chlamydia	CERTIFICATE OF EFS WEB FILING I hereby certify that this correspondence is being electronically filed via the USPTO Electronic Filing System (EFS Web) on this 1st day of December, 2008. /Marie Mikolainis/ 12/01/2008 Marie Mikolainis Date

APPELLANTS' REPLY BRIEF

Board of Patent Appeals and Interferences
U.S. Patent and Trademark Office
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

This Brief is submitted in accordance with 37 C.F.R. § 41.41 and is submitted in response to the Examiner's Answer mailed October 2, 2008. This Reply Brief is submitted within two months from the mailing date of the Examiner's Answer. Appellant requests favorable consideration for the reasons addressed herein.

Concurrently submitted herewith is a "Request for Oral Hearing" accompanied by the fee set forth in § 41.20(b)(3), both of which are submitted within two months from the date of the Examiner's Answer.

I. INTRODUCTION

The Examiner's Answer in response to applicant's argument that the present claims are enabled boils down to two specific points:

1. The specification does not contain a specific example of immunizing an animal with a single *Chlamydia psittaci* antigen (i.e., protein); and
2. One of an admittedly high level of skill in the art would not view as enabling a disclosure that clearly enables immunization of an animal with

a DNA or polynucleotide sequence encoding the claimed antigens (i.e., protein); and immunization of an animal using a pool of the claimed antigens (i.e., proteins).

Appellants' Reply is simple and straightforward: "Compliance with the enablement requirement of 35 U.S.C. § 112, first paragraph, does not turn on whether an example is disclosed," MPEP § 2164.02. The specification need not contain an example if the invention is otherwise disclosed in such a manner that one skilled in the art will be able to practice the invention without an undue amount of experimentation, In re Borkowski, 422 F.2d 904, 908, 154 USPQ 642, 645 (CCPA 1970). Since an evaluation of the In re Wands factors clearly demonstrates that any experimentation would not be "undue," judgment in favor of the appellant is appropriate.

II. THE WANDS FACTORS DEMONSTRATE ENABLEMENT UNDER 35 U.S.C. § 112, ¶1

A. The Nature of the Invention and Breadth of the Claims

The nature of the invention is a method for immunizing an animal comprising administering to the animal a *Chlamydia psittaci* antigen having a specific SEQ ID NO. in an amount effective to induce a protective immune response against *Chlamydia psittaci*. As noted, prior art antibiotic treatment for Chlamydia infection is not practical, and conventional vaccines are inconsistent. Therefore, a vaccine for the prevention of the disease in animals is desirable.

The appealed claims are directed to a method of immunizing an animal comprising the step of: administering a *Chlamydia psittaci* antigen to an animal in an amount effective to induce an immune response against *Chlamydia psittaci*; wherein the *Chlamydia psittaci* antigen comprises an amino acid sequence as set forth in SEQ ID NO:7. The dependent claims are more narrow, with some claiming a method that further comprises administering a second *Chlamydia psittaci* antigen to an animal in an amount effective to induce an immune response against *Chlamydia psittaci*; wherein the second *Chlamydia psittaci* antigen comprises an amino acid sequence set forth as (SEQ ID NOS:9, 11, 13, 17, 23 or 27), *see*, claims 94-95.

B. The Specification Presents Ample Guidance and Direction Along with Working Examples

To be clear, appellant believes that the Examiner's position with respect to undue experimentation is that "One of skill in the art would require guidance, in order to make or use the claimed invention in a manner reasonable in correlation with the scope of the claims.

Without proper guidance, experimentation is undue." (Answer, p. 6). As will be demonstrated herein, the specification of the present application is replete with guidance to one of ordinary skill in the art as to how to make and use the claimed invention.

The Examiner downplays the significance of the results shown in Fig. 5 of the present application in an effort to support the "lack of guidance" argument. However, the experiment associated with Fig. 5 is at the crux of the enablement issue in dispute. The experiment associated with the results demonstrated in Fig. 5 of the present application is both a working and prophetic example. In the present specification, the inventors used Expression Library Immunization (ELI) to identify vaccine candidates. The goal was to identify, among all *Chlamydia psittaci* proteins, polynucleotide and polypeptide fragments that elicited protective immunity. In order to identify the particular sequences or fragments that provided an immune response, the inventors conducted a series of experiments with mice as detailed in Fig. 5 and the associated discussion of the present application (*see*, pp. 64-89). These genetic immunization experiments included administering particular DNA (i.e., polynucleotide) sequences to mice to determine whether such sequences induced an immune responsive against *Chlamydia psittaci*. This experimental procedure is also discussed in the Declarations of Dr. Kaltenboeck which are annexed to appellant's opening brief in the evidence appendix.

> The Examiner chooses to characterize the results in Fig. 5 as follows:
>
> "To address Appellant's comment's regarding Figure 5, it should be noted that this figure merely discloses the results of protection assays of testing 14 single gene fragments in round 4 of screening (not antigen or protein as recited in the claimed method) provide some level of protection when administered to mice." (Answer at p. 17).

However, there is more than "some level" of protection that is provided by the identified genes and gene fragments; it is a level of protection that is <u>better than what is naturally available</u> through a conventional vaccine (*see*, e.g., Fig. 5 which demonstrates the relative protection of particular gene fragments relative to challenged and vaccinated controls).

The results demonstrated in Fig. 5 and the associated discussion in the specification clearly indicate that genetic immunization achieved protection from *Chlamydia psittaci* infection <u>better than what was achievable from natural vaccination</u>. A positive genetic immunization control pool <u>also protected better</u> than what was naturally achievable. Accordingly, from the genetic immunization experiment detailed in Fig. 5, particular genes and

gene fragments that were effective to induce an immune response against *Chlamydia psittaci* were specifically identified.

In fact, the most highly protective gene identified was Gene No. 1 which corresponds to CP4#1 in Table 2 in Fig. 6 of the present application. As detailed throughout this prosecution and in the appellants' opening brief, CP4#1 corresponds to SEQ ID NOS. 6-9 (*see*, Appellant's First Amended Brief on Appeal at pp. 15-17).

Subsequently, the sequences of all of the identified protective gene fragments were analyzed, the full *Chlamydia psittaci* genes were isolated, and the position of the fragments within the full genes were determined. The genes were then characterized for gene terminology and function by homology search. The results are detailed in Fig. 6, and are described in Example 6 with a summary in Table 2 (p. 74). A complete listing of all sequences, both polynucleotide and polypeptide, with sequence ID numbers are provided in Table 3, pp. 75-80, of the present application.

In disparaging the present specification for lack of guidance to one of ordinary skill in the art, the Examiner cites MPEP § 2164.01(b) which states:

> "A key issue that can arise when determining whether the specification is enabling is whether the starting materials or apparatus necessary to make the invention are available. In the biotechnical area, this is often true when the product or process requires a particular strain of microorganism and when the microorganism is available only after extensive screening. The Court in In re Ghiron, 442 F.2d 985, 991, 169 USPQ 723, 727 (CCPA 1971), made clear that if the practice of a method requires a particular apparatus, the application must provide a sufficient disclosure of the apparatus if the apparatus is not readily available. ... The same can be said if certain chemicals are required to make a compound or practice a chemical process. In re Howarth, 654 F.2d 103, 105,210 USPQ 689,691 (CCPA 1981)." (Answer at p. 12).

In reply, appellant respectfully asserts that the starting material for the claimed method of immunizing using one *Chlamydia psittaci* is clearly disclosed. The specification, as noted above, advises that the DNA sequences identified in the experiments associated with Fig. 5 effect immunization in mice. Fig. 6 identifies the particular gene fragments in genes that correlate to the CP4# numbers in Fig. 5. Table 3 correlates the CP4# numbers, not only to the genes, but also to the full length and fragment DNA, and the protein sequences that correlate to the immunizing gene fragment identified in Fig. 5. Therefore, the specification does include disclosure of the precise amino acid sequence for the claimed method. The specification also

contains an extensive discussion on materials used for the vaccination method claimed (*see*, specification at pp. 7-8, 23-31, 58-62, 85-86).

One of ordinary skill in the art will understand that it is the protein (i.e., antigen) expressed by the gene fragments that elicits immune response in the animal, not the DNA of the gene fragments itself. Thus, for the Examiner to dismiss the results of Fig. 5 is disingenuous because it demonstrates to one of ordinary skill in the art that the identified DNA sequences encode for claimed antigens that do, in fact, induce an immune response against *Chlamydia psittaci* in an animal, *see*, In re Wallach, 378 F.3d 1320, 1334, 71 USPQ2d 1939 (Fed. Cir. 2004) ("It is a routine matter to convert back and forth between an amino acid sequence and the sequences of nucleic acid molecules that encode it."). Additionally, the genetic immunization experiment of Fig. 5 provides exact guidance to one of ordinary skill in the art to conduct a simple experiment using well known recombinant DNA technology to confirm the efficacy of the claimed antigens, *see*, Babiuk (Vaccine 17, 1587-1595 at p. 1588):

> "By identifying the proteins involved in inducing protective immunity and isolating the gene coding for these proteins it is possible to use recombinant DNA technology or synthetic peptide technology to produce sufficient quantities of these protective epitopes for incorporation into vaccines." (Babiuk at p. 1588).

Additionally, the specification is replete with guidance to one of ordinary skill in the art as to how a protein (i.e., antigen) vaccine may be realized using only the knowledge of an identified, protective gene fragment. The specification at p. 18 specifically instructs:

> "The present invention provides polynucleotides encoding antigenic *Chlamydia psittaci* polypeptides capable of inducing a protective immune response in vertebrate animals and for use as an antigen to generate *anti-Chlamydia psittaci* or other pathogen antibodies. In certain instances, it may be desirable to express *Chlamydia psittaci* polynucleotides encoding a particular antigenic *Chlamydia psittaci* polypeptide domain or sequence to be used as a vaccine or in generating *anti-Chlamydia psittaci* or other pathogen antibodies. Nucleic acids according to the present invention may encode an entire *Chlamydia psittaci* gene, or any other fragment of the *Chlamydia psittaci* sequences set forth herein. The nucleic acid may be derived from genomic DNA, *i.e.*, cloned directly from the genome of a particular organism. In other embodiments, however, the nucleic acid may comprise complementary DNA (eDNA). A protein may be derived from the designated sequences for use in a vaccine or to isolate useful antibodies." (present application at p. 18).

The specification further explains:

> "For the purposes of the present invention a *Chlamydia* polypeptide used as an antigen may be a naturally-occurring *Chlamydia* polypeptide that has been extracted using protein extraction techniques well known to those of skill in the art. In particular embodiments, a *Chlamydia* antigen is identified by ELI and prepared in a pharmaceutically acceptable carrier for the vaccination of an animal against *Chlamydia* infection.
>
> In alternative embodiments, the *Chlamydia* polypeptide or antigen may be a synthetic peptide. In still other embodiments, the peptide may be a recombinant peptide produced through molecular engineering techniques. The present section describes the methods and compositions involved in producing a composition of *Chlamydia* polypeptides for use as antigens in the present invention." (present application at p. 23).

Additionally, further discussion of use of *Chlamydia psittaci* polypeptides as antigens is present in the application at pp. 23-31.

Contrary to the Examiner's assertions, it is abundantly clear that one of ordinary skill in the art would reasonably conclude that a DNA vaccine and a protein (i.e., antigen) vaccine would behave in an identical manner when administered to an animal. The function of a gene (which is comprised of a polynucleotide DNA sequence) is to specify the structure of a protein. Thus, if a DNA vaccine elicits an immune response, one of ordinary skill in the art would conclude that the protein encoded by the DNA in that vaccine would also elicit an identical immune response because the expression of the DNA vaccine *in vivo* into its corresponding protein is what invoked the immune response of the DNA vaccine in the first place. In fact, the acknowledged interrelationship between DNA sequences and the corresponding protein is the precise basis for recombinant DNA vaccine technology that is well known in the art. It is well known in the art that recombinant DNA techniques are useful in any situation where protein antigens need to be synthesized in large and pure quantities (*see*, e.g., Immunology: An Introduction, Second Edition by Ian R. Tizard, Copyright 1988).

The issue as to which particular genes and antigens provide protection are specifically answered by the results detailed in Figs. 5 and 6, as well as Tables 2 and 3 of the present application, as described above. Appellant particularly notes that correlation between the CP4# numbers in the particular SEQ ID numbers is set forth in detail in the prosecution history of the present application. Particularly, with respect to the claims at issue, SEQ ID NO:6 is the original DNA fragment identified as protective in the experiment of Fig. 5, identified

therein as CP4#1. SEQ ID NO:7 is the polypeptide fragment corresponding to the gene fragment of SEQ ID NO:6; SEQ ID NO:8 is the full length DNA gene that includes the gene fragment of SEQ ID NO:6; and SEQ ID NO:9 is the full length polypeptide sequence of SEQ ID NO:8.

In sum, the teachings of the experiments detailed above indicate that mice were administered a genetic immunization in an amount effective to induce an immune response. The genetic immunization comprised a single gene fragment that, when transcribed into its corresponding antigen (i.e., protein) elicited an immune response in the mice. Several genes were demonstrated to be more effective than conventionally vaccinated mice, particularly the genes identified as CP#1-CP#4, all of which correspond to the currently claimed antigens in the independent and dependent claims (*see*, Table 3, pp. 75-80 of the present application).

Accordingly, appellant respectfully asserts that the Examiner is incorrect that the instant specification has only one example that relates specifically to the vaccination of animals (*see*, Answer at p. 5, L1-2). Mice were vaccinated in Example 4 and the results shown in Figs. 5 and 6. In addition to Example 8, bovines were also vaccined in Example 9.

Given the fact that the Examiner admits that the level of skill in the art is "quite high (post-doctoral level)" (Answer at p. 6), it is clear that one of ordinary skill in the art would use the guidance of the experiments detailed in Fig. 5, along with the additional teachings of the specification noted above, to make and use a *Chlamydia psittaci* protein vaccine comprising one single *Chlamydia psittaci* antigen in an amount effective to induce an immune response. One of ordinary skill in the art would also use the teachings of the specification to realize a method of immunizing an animal comprising the step of: administering a *Chlamydia psittaci* antigen to an animal in an amount effective to induce an immune response against *Chlamydia psittaci*, wherein the *Chlamydia psittaci* antigen comprises an amino acid sequence set forth at SEQ ID NO: 7.

C. The State of the Prior Art Indicates High Predictability

In contesting appellants' argument that any necessary experimentation is not undue, the Examiner makes conclusory statements that the art is unpredictable, relying on Sato et al (Science Vol. 273, July 19, 1996, p. 352-354) that there is a lack of success in the art. Respectfully, these conclusory statements are incorrect.

The Examiner cites Sato et al for the premise that DNA vaccines do not necessarily induce an immune response to the encoded antigen. However, this premise clearly

lacks support in the article and is based on taking one sentence in the abstract out of context. Sato et al specifically states:

> "Intramuscular (1) or intradermal (2) administration of pDNA expression vectors causes intracellular synthesis of the encoded proteins and induction of long-lasting cellular and humoral immune response." (Sato et al at p. 352).

Additionally, the experiment detailed in the Sato et al article was performed to establish that manipulation of a vector to provide large amounts of the expressed antigen does not produce a stronger immune response. In this regard, Sato et al specifically states:

> "Our findings indicate that immunogenic pDNA may be divided conceptually into two distinct units: *a transcription unit that directs antigen synthesis* and an adjuvant unit in the plasmid backbone that elicits the production of type-1 IFN and IL-12 in the transfected skin keratinocytes and ACSs. For this reason, manipulation of the transcription unit within the pDNA *to yield higher levels of antigen expression* does not necessarily produce a stronger immune response. Both the localization and the precise sequence of the ISS within the plasmid backbone are also important for DNA vaccination. Thus, the potential ISS, 5'-GACGTC-3', and 5'-AGCGCT-3' in the pKCB-Z transcription unit did not have sufficient adjuvant activity in vivo (Fig. 1). In contrast, the addition of one or two repeats of the 5'-AACGTT-3' sequence to the noncoding region of the pKCB-Z backbone enhanced the immune response to ß-Gal in a 'gene dosage'-related fashion (compare pKISS-1-CB-Z with pKISS-2-CB-Z in Table 1)." (Sato et al at p. 354). (emphasis added)

Accordingly, the Examiner's conclusion is unfounded, particularly taken in light of the fact that Sato et al explicitly states that expression of DNA in plasmid vector causes protein synthesis that positively induces an immune response. The Examiner's conclusions regarding Sato et al are entirely unfounded.

Furthermore, the other articles cited by appellant in the initial brief support the fact that a protein vaccine will behave in the same manner as a DNA vaccine does in an animal. Tang et al (Nature 356, 151-154) specifically states:

> "To produce an immune reaction against a foreign protein usually requires purification of that protein, which is then injected into an animal. The isolation of enough pure protein is time-consuming and sometimes difficult. Here we report that such a response can also be elicited by introducing the gene encoding a protein directly into the skin of mice." (Tang et al at p. 151).

Babiuk (Vaccine 17, 1587-1595), in discussing the efficacy of sub-unit vaccines, specifically states:

> "By identifying the proteins involved in inducing protective immunity and isolating the gene coding for these proteins it is possible to use recombinant DNA technology or synthetic peptide technology to produce sufficient quantities of these protective epitopes for incorporation into vaccines." (Babiuk at p. 1588).

Ellis (Vaccine 17, 1596-1604) also advocates for the use of protein vaccines based on genomic research:

> "Developing a (purified) protein-based vaccine is the strategy of choice for many pathogens in which a polypeptide contains protective epitopes and assuming that an inactivated vaccine is technically not feasible or undesirable. In addition to traditional ways of discovering vaccine antigens, there are newer enabling technologies such as genomics which also are being employed to identify novel antigens." (Ellis at 1599).

Thus, the literature alone indicates a substantial success in the prior art of utilizing proteins (i.e., antigens) isolated from identified, protective genes. The extensive discussion in the specification noted above further buttresses this conclusion. Moreover, the predictability that a protein (i.e., antigen) vaccine will be efficacious if a corresponding DNA vaccine's efficacious is extremely high, as noted in the articles above. Therefore, the evidence demonstrates that the state of the prior art indicates high predictability for any experimentation that may be deemed necessary.

Accordingly, for all the reasons set forth above, appellants respectfully assert that one of ordinary skill in the art has sufficient guidance to make and use the claimed invention in a manner reasonable in correlation with the scope of the claims. Moreover, an evaluation of the Wands factors as set forth in appellants' opening brief, and further detailed above, clearly demonstrates that any experimentation necessary to realize the claimed invention would certainly not be undue. Therefore, appellants respectfully assert that claims directed to administering a *Chlamydia psittaci* antigen to an animal in an amount effective to induce an immune response against *Chlamydia psittaci*; wherein the *Chlamydia psittaci* antigen comprises an amino acid sequence as set forth in SEQ ID NO:7 are clearly enabled to one of ordinary skill in the art by the present specification.

III. OTHER CONSIDERATIONS

A. The Prosecution History Provides Context to the Present Enablement Rejection

The Examiner dismisses applicants' review of the prosecution history as "not a requirement in an appeal brief." Applicants included the prosecution history discussion in their opening brief to demonstrate how the Examiner has continuously changed tact in the present case and that the current enablement rejection contrasts the positions taken by the Examiner earlier in the prosecution.

Applicant again reiterates that the Examiner stated three times during the prosecution of the present application that:

> "The rejection under 35 U.S.C. § 112, first paragraph is maintained for [claims] 92 and 96-99 for the reasons set forth on pages 2-7, ¶4 of the Final Office Action. The rejection was on the grounds that the claims **while being enabling for a method of immunizing an animal comprising providing to the animal; at least one Chlamydia antigen corresponding to Sequence ID No. 9 or Sequence ID No. 7 and further comprising a second Chlamydia antigen corresponding to Sequence ID No. 11 or Sequence ID No. 13** does not reasonably provide enablement for variants of the Sequence ID No. 7, 9, 11 or 13 encompassed by the claims that can be used in the claimed method." (*see*, Office Action mailed 07/28/06 at p. 2) (bold added, underline in original).

Appellants reiterate that the Examiner's continued statement to this effect led applicants to believe that a method for immunizing an animal in an amount effective to induce an immune response to *Chlamydia psittaci*, wherein the *Chlamydia psittaci* antigen comprises amino acid or polypeptide sequence set forth in SEQ ID NOS:7, 9, 11 or 13 was clearly enabled. It was not until seven years into the prosecution after appellant cooperated with the examiner to narrow the claims that the issue involving whether or not a single sequence was enabled was first identified by the Examiner. This convoluted and extrapolated prosecution of the present application is exactly the opposite of a "compact prosecution" discussed in MPEP § 2161.04.

B. Appellants' Arguments Regarding Allowability of Dependent Claims Not Addressed

Appellants' First Amended Brief on Appeal argued that dependent claims 94 and 95 should be allowable since both claims are directed to administering at least two separate antigens, and are not directed to administering a single antigen. The Examiners consistently argued that the basis for the enablement rejection is that the specification does not provide enablement for a method of immunizing an animal comprising the step of administering a single *Chlamydia psittaci* antigen to an animal in an amount effective to induce an immune response

against *Chlamydia psittaci*; wherein the *Chlamydia psittaci* antigen comprises the amino acid sequence set forth as SEQ ID NOS:7, 9, 11 and 13 (examined sequences) (Examiner's Answer at p. 30). The Examiner further states that: "The instant specification has further shown enablement for a protein vaccine which comprises full-length *Chlamydia psittaci* proteins and/or protein fragments. See Example 9 of the specification. (Examiner's Answer at p. 4). However, the Examiner disparages the results of Experiment 9 by asserting that one skilled in the art cannot ascertain whether one single gene or protein or a combination of genes or proteins provide the protection described in Examples 8 and 9 of the instant specification.

As set forth above, it is applicants' position that the results of the experiment demonstrated in Figure 5 reveals several gene fragments that confer protection against *Chlamydia psittaci*. A further analysis detailed in the specification correlates those protective fragments with particular genes, and also translates the nucleotide sequence of those genes into amino acid sequences. Accordingly, several genes and proteins that provide protection have been identified in the specification. One of ordinary skill in the art would expect any one or any combination of these genes and proteins to provide protection described in Examples 8 and 9 of the present specification.

In light of the Examiner's admission that the instant specification has shown enablement of protein vaccine which comprises full length *Chlamydia psittaci* proteins and/or protein fragments, appellants assert that claims 94-95 should be allowable since they are directed to administering at least two separate antigens, and are not directed to administering a single antigen.

Appellant respectfully notes that the Examiner has not addressed this issue in the Examiner's Answer and, therefore, respectfully requests favorable consideration of this issue.

C. Appellants Are Willing to Make the Suggested Amendments to Overcome § 101 and § 112 Issues

Applicant again notes that it is willing to make proper amendments to obviate the §§ 101 and 112 rejections noted by the Examiner. With respect to the § 101 rejection, the Office Action dated January 28, 2008 indicates that "This rejection may be obviated, if the claims are amended to an 'isolated or purified' *Chlamydia psittaci* antigen." Applicants intend to make the proposed amendment when the enablement issues are resolved through this appeal.

With respect to the § 112 issue first brought up by the Examiner in the Reply Brief, applicants intend to change the language "preparing" in claims 104-106 to the term

"administering" to obviate the rejection under 35 U.S.C. § 112, ¶2, once the present issues on enablement are resolved.

IV. CONCLUSION

Favorable consideration of this appeal and removal of the rejection under 35 U.S.C. § 112, ¶1, for lack of enablement is earnestly solicited.

Respectfully submitted,

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